Oxiplex®

PMA # P070023

Orthopaedic and Rehabilitation Devices

Advisory Panel Presentation

July 15, 2008

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Oxiplex®

Introduction & Device Description

John Krelle
President and CEO
FzioMed, Inc.

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Agenda

Introduction & Device Description.....	John Krelle
Unmet Clinical Need.....	Alfred Rhyne, MD
Pre-Clinical & Feasibility Study.....	Gere diZerega, MD
IDE Pivotal Clinical Study	
Study Design.....	Ron Ehmsen, ScD
Safety.....	Paul Arnold, MD
Statistical Methods.....	Richard Chiacchierini, PhD
Effectiveness.....	Scott Blumenthal, MD
Summary	

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Oxiplex®

- Clear, viscoelastic gel
- Coats & protects neural tissues
- 3mL gel in syringe
- Flexible applicator
- Ready to use
- Single use only

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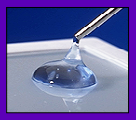
Oxiplex® Intraoperative Gel

- Composition
  - Carboxymethylcellulose (CMC)
  - Polyethylene oxide (PEO)
  - CMC & PEO used extensively in implantable medical devices and pharmaceuticals
- Bioabsorbable
- Non-pyrogenic
- No animal or bacterial components
- No color additives



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Oxiplex® Proposed Indication for Use

- A surgical adjuvant during lumbar laminectomy, laminotomy, or discectomy to improve patient outcomes by reducing postoperative leg pain, back pain and neurological symptoms.
- First-of-a-kind indication

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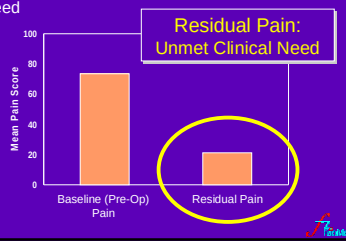
Study Goals

- Demonstrate safety
- Reduce residual pain & symptoms
  - Discectomy is usually very successful
  - Residual pain & symptoms often persists
  - An unmet clinical need



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Post-Surgical Pain & Symptoms

- Complex situation
- Multiple co-morbidities & clinical factors complicate
  - Clinical presentation
  - Measurement

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Approved Statistical Method: Multivariate Analysis

- Multivariate analysis is most appropriate for this complex clinical situation
- Pre-specified by Sponsor in Statistical Analysis Plan (SAP)
- Unconditionally approved by FDA as the analytical method for the Oxiplex pivotal study

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Study Success

- Across all effectiveness measures, all patients treated with Oxiplex had greater improvement than Controls, demonstrating consistent clinical benefit from the use of Oxiplex.
- Multivariate analysis allowed identification of an important patient subgroup which comprised the majority in the Oxiplex study: Patients with severe baseline back pain
- Target: 33% difference (reduction in leg pain) between groups achieved in this subgroup

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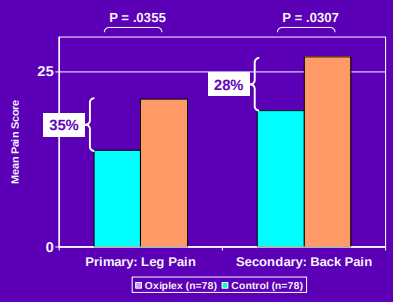
Oxiplex Reduced Residual Leg & Back Pain

Patients with Severe Baseline Back Pain



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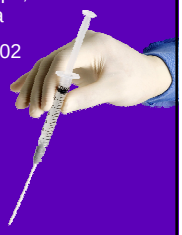
Oxiplex® Status

- Approved for sale in 49 countries in Europe, Asia, South America, Australia & Canada
- Over 100,000 spine procedures since 2002
- Distributed outside U.S. through

Medtronic

DePuySpine
a Johnson & Johnson company



- Safety demonstrated through international post-market surveillance

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Oxiplex®

Clinical Presentation & Unmet Need

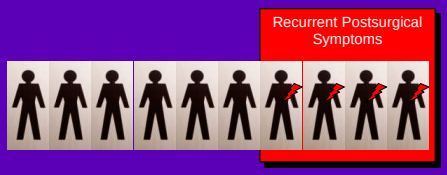
Alfred L. Rhyne, M.D.
OrthoCarolina Spine Center
Charlotte, NC

Spine Surgery Success & Failure

- Lumbar discectomy surgery is generally a successful procedure
- Reported success rates from 60% to 90%
- Nonetheless….

Unmet Clinical Need

- Substantial numbers of patients (up to 40%) experience residual or recurrent pain and neurological symptoms following surgery
- Re-operation rates range from 5% to 20%



Complexity of Residual Pain in Spine Surgery Patients

- Multifactorial
  - Numerous potential etiologies
- Multidimensional
  - Each patient presents with unique combination of symptoms
- Confounded by numerous clinical factors

Factors that Influence Back Pain Outcomes

Clinically Relevant Covariates

Baseline
Demographics
Workman's compensation
Location of pain
  Back
  Radicular
Severity of pain
  Leg pain
  Back pain
Prior therapies
  Number of epidural injections
  Anti-inflammatory medication
  Use of opioid analgesics
  Extent of chiropractic therapy
  Physical therapy
Subject's perception of pain & symptoms
Duration of symptoms
Nerve root tension (positive leg raise)
Motor loss (weakness)
Sensory loss (paresthesia)
Discogenic pain
Neurological deficit
  Asymmetrical depressed reflex
  Decreased sensation dermatomal distribution
  Weakness in myotomal distribution
Nerve root irritation
Type of disc herniation (protrusion, extrusion, sequestered fragment)
Location of herniation (level relative to vertebral body)

Intraoperative
Surgical time
Micro or Macro surgery

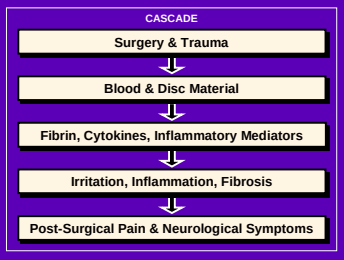
Clinical pain from disc herniation is complex and multifactorial.

 Spine Patient Outcomes Research Trial (SPORT), JAMA 296:2441, 2006; JAMA 296:2541, 2006; Spine 33:428, 2008; Spine 33:991, 2008.

2 Categories of Pain Mechanisms

- Mechanical mechanisms:
  - Incomplete decompression
  - Recurrent herniation
  - Stenosis
  - Instability
- Biological / Biochemical mechanisms:
  - Fibrin
  - Cytokines
  - Pro-inflammatory mediators
  - Edema, ischemia, cellular injury
  - Wound exudates, neurotoxins

Cascade of Biological & Biochemical Irritants



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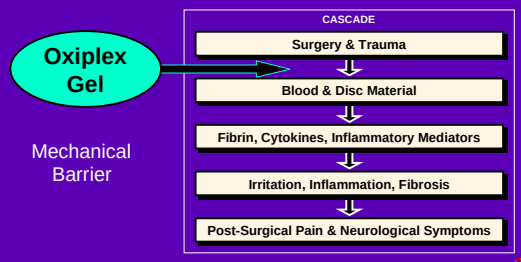
- Oxiplex is intended as a temporary mechanical barrier, providing physical separation of tissues to reduce exposure to irritants which may lead to pain.



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Unmet Need

- There is no FDA-approved surgical adjuvant indicated for the reduction of pain and neurological symptoms in lumbar disc surgery.
- Surgeons' attempts to protect the nerve root for this purpose include:
  - Fat grafts
  - Products not designed for this indication (Gelfoam, sealants and dural regeneration sheets)

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Oxiplex® Gel

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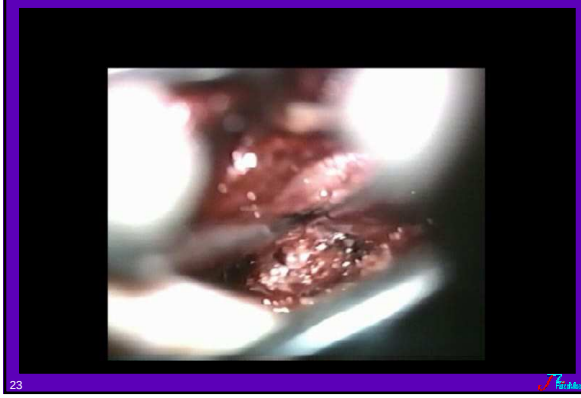
Oxiplex® Intraoperative



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Preserve Surgical Excellence

- A product which, when applied to epidural tissues prior to close of surgery, acts as a safe, mechanical barrier
  - Separates tissue
  - Protects nerve root during healing process
- A product which improves outcomes such as pain and neurological symptoms

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Oxiplex®

Preclinical Studies

Gere S. diZerega, M.D.
Medical Director
FzioMed, Inc.

Preclinical Safety & Biocompatibility Studies

Sensitization	• Maximization Sensitization
Irritation	• Intracutaneous Reactivity
Implantation	• Muscular Implant Test
Cytotoxicity	• MEM Elution Assay
Systemic Toxicity	• Systemic Injection
Subchronic Toxicity	• 30 & 45 day Subchronic Implant (1x, 5x, 10x doses)
Chronic Toxicity	• 120-day Implant
Genotoxicity	• AMES Test • Chromosomal Aberration
Pyrogenicity	• Material Mediated Pyrogen
Hemolysis	• Hemolytic Potential Tested
Microbiology	• Kinetic-Chromogenic Limulus Assay (LAL) (≤0.06 EU/mL (CSF exposure)

Preclinical Safety & Biocompatibility Studies

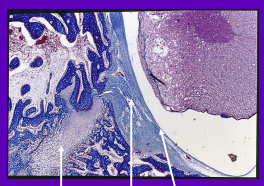
- Carcinogenic toxicity
  - Components are non-carcinogenic
  - Oxiplex cleared within 30 days in animal studies
  - Oxiplex is a single-use product
- Immunotoxicity
  - No evidence of immunologic response in any of the acute or chronic toxicity or sensitization studies performed

Preclinical Dural Healing Study

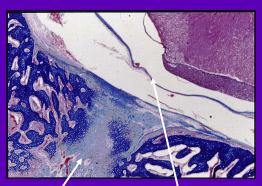
- 6 rabbits for each group
  - Oxiplex Gel
  - Control (no product)
- Two level laminotomy
- 2mm dural nick
- Euthanized at 14 days post-surgery
- Gross observation and histology

Histological Results (14 Days)

Control



Oxiplex



Preclinical Dural Healing Study

Oxiplex Did Not Impair Dural Healing or Induce Inflammation

	Number of Histological Sections			
Group	**Not Healed**	**Partially Healed**	**Completely Healed**	**Inflammatory Response**
Control (n=34)	7 20.6%	2 5.9%	25 73.5%	0 of 6
Oxiplex® Gel (n=35)	3 8.6%	0 0%	32 91.4%	0 of 6

n = # of histological sections

* Rodgers et al. Evaluation of FzioMed adhesion barrier gel on dural healing in a model of epidural fibrosis in rabbits. CNS 2003, Denver.

Summary of Preclinical Safety Studies

- Biocompatible
- Normal histology
- Oxiplex allowed normal healing
  - Oxiplex did not inhibit dural healing
  - Oxiplex did not inhibit bone repair
  - Oxiplex did not inhibit normal wound healing
- Non-inflammatory
- Conclusion: Oxiplex safe in preclinical studies

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Oxiplex®

Clinical Feasibility Study

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Oxiplex® Clinical Feasibility Study

- Objective
  - Evaluate safety & symptoms following single-level lumbar disc surgery
- Prospective, randomized, single-blinded
- 4 Sites
- 35 Subjects
  - Treatment: Surgery + Oxiplex (N=23)
  - Control: Surgery Alone (N=12)

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Feasibility Study Measures

- Clinical evaluation
- Laboratory analyses
- MRI at 3 months
- Quality of Life postoperative assessments
  - 1, 3, 6 and 12 months
  - Oswestry Disability Questionnaire (ODI)
  - Lumbar Spine Outcomes Questionnaire (LSOQ)

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Lumbar Spine Outcomes Questionnaire (LSOQ)

- LSOQ developed in response to NIH-RFA

National Institutes of Health
The Nation's Medical Research Agency

Donlin Long, MD	Johns Hopkins University School of Medicine
Robert Boyd, MD	Massachusetts General Hospital
Edgar Dawson, MD	UCLA
Russell Hardy, MD	Case Western Reserve
James T. Robertson, MD	University of Tennessee
Clark Watts, MD	University of Missouri
George Sypert, MD	University of Florida

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LSOQ Design & Validation

- 56 Questions
- Validated (2,539 subjects)
  - External & internal constructs
  - Correlated to ODI & SF-36
  - Responsiveness
  - Reliability
- Consistent results (6, 12 and 24 months)
- Clinical significance = patient satisfaction

JOHNS HOPKINS MEDICINE

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LSOQ Important Feature

- Provides disease-specific information on:
  - Leg Pain
  - Back Pain
  - Leg Weakness
  - Physical Symptoms
  - Activities of Daily Living
  - Patient Satisfaction
  - Disability Days

BenDebba M, dZerega GS, Long DM. The Lumbar Spine Outcomes Questionnaire: its development and psychometric properties. Spine Journal 2007;7: 188-132.

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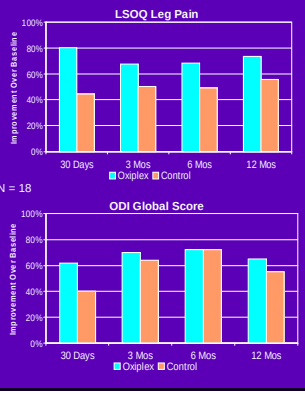
Feasibility Study Key Results



N = 18

Summary:

1. Oxiplex subjects with severe pain at baseline had greater improvement than Controls.
2. LSOQ results at 6 months were similar to LSOQ results at 12 months.
3. LSOQ more discriminating than ODI.

- Kim, Wang, Robertson, Brodke, et al. Spine 2003;28:1080-1088.
- Kim, Wang, Robertson, Brodke, et al. Neurosurgical Focus 2004;17 (1): Clinical Pearl 1.

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Feasibility Study

LSOQ Case Report Form: Leg Pain Questions

9. Which word best describes the severity of the pain in your legs or buttocks, when it hurts the most ?
No pain ☐1 Mild ☐2 Discomforting ☐3 Distressing ☐4 Horrible ☐5 Excruciating ☐6
10. Which word best describes the severity of the pain in your legs or buttocks, when it hurts the least ?
No pain ☐1 Mild ☐2 Discomforting ☐3 Distressing ☐4 Horrible ☐5 Excruciating ☐6
11. Which word best describes the severity of the pain in your legs or buttocks, at this moment ?
No pain ☐1 Mild ☐2 Discomforting ☐3 Distressing ☐4 Horrible ☐5 Excruciating ☐6
12. Which word best describes the severity of the pain in your legs or buttocks, on average, on a typical day ?
No pain ☐1 Mild ☐2 Discomforting ☐3 Distressing ☐4 Horrible ☐5 Excruciating ☐6
13. Which word best describes the severity of the pain in your legs or buttocks, at the end of an active day ?
No pain ☐1 Mild ☐2 Discomforting ☐3 Distressing ☐4 Horrible ☐5 Excruciating ☐6
14. Which word best describes the severity of the pain in your legs or buttocks, when you first wake up from a night's sleep ?
No pain ☐1 Mild ☐2 Discomforting ☐3 Distressing ☐4 Horrible ☐5 Excruciating ☐6

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Feasibility Study

LSOQ Case Report Form – Leg Pain Before Surgery

BASELINE

9. Which word best describes the severity of the pain in your legs or buttocks, when it hurts the most ?
No pain ☐1 Mild ☐2 Discomforting ☐3 Distressing ☐4 Horrible ☐5 Excruciating ☒6
10. Which word best describes the severity of the pain in your legs or buttocks, when it hurts the least ?
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SCORE: 77

((Sum of Questions 9-14) – 6] x 100) ÷ 30 = 77

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Feasibility Study

LSOQ Case Report Form – Leg Pain at 6 Months

6 MONTHS

9. Which word best describes the severity of the pain in your legs or buttocks, when it hurts the most ?
No pain ☐1 Mild ☐2 Discomforting ☒3 Distressing ☐4 Horrible ☐5 Excruciating ☐6
10. Which word best describes the severity of the pain in your legs or buttocks, when it hurts the least ?
No pain ☒1 Mild ☐2 Discomforting ☐3 Distressing ☐4 Horrible ☐5 Excruciating ☐6
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SCORE: 23

((Sum of Questions 9-14) – 6] x 100) ÷ 30 = 23

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Oxiplex® Feasibility Study Results

- No adverse events attributed to the device
- No abnormal laboratory values
- MRIs showed no additional risk to Oxiplex-treated subjects
- No abnormal physical findings
- Pain reduction comparable at 6 and 12 months

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Feasibility Study Conclusion

FDA Executive Summary:

- "Because the results from the pilot study did not raise safety concerns, FDA allowed the Sponsor to initiate a new pivotal study to study the safety and efficacy of Oxiplex in a larger population."

Oxiplex®

Pivotal Clinical Study

IDE #G000226
FzioMed Clinical Protocol #FZ-SP002

Ron Ehmsen, Sc.D.
V.P. Clinical and Regulatory Affairs
FzioMed, Inc.

Pivotal Clinical Study

- Randomized, Third-Party Blinded, Multicenter Clinical Trial to Determine the Safety and Effectiveness of Oxiplex/SP Gel for the Reduction of Pain and Symptoms Following Lumbar Disc Surgery

Study Objectives	
Primary Objectives	1. To evaluate the safety of using Oxiplex in lumbar disc surgery. 2. To evaluate the efficacy of Oxiplex in the reduction of postoperative pain and symptoms beyond that achieved by surgery alone.
Secondary Objective	To evaluate pain, symptoms, disability, patient satisfaction, and quality of life measures relevant to the postsurgical condition of subjects undergoing lumbar surgery.

Pivotal Clinical Study

Safety Variables	
Primary Safety Variables	The occurrence of adverse events, including surgical complications, categorized using the MedDRA coding system (Version 7.1).
Secondary Safety Variable	1. To evaluate the changes in laboratory results, physical and neurological examinations and vital signs throughout the study. 2. To evaluate reoperations at the lumbar level. 3. To evaluate the use of concomitant therapies.
Effectiveness Variables	
Primary Effectiveness Variable	Improvement in Leg Pain from baseline to follow-up visits (1, 3 and 6 months), as measured by the LSOQ.
Secondary Effectiveness Variable	Improvement from baseline to follow-up visits (1, 3, 6 months), as measured by the LSOQ in: 1. Back pain 2. Leg weakness 3. Physical symptoms 4. Patient satisfaction (LSOQ measure of clinical effectiveness) 5. Disability days 6. Activities of daily living

Pivotal Clinical Study Design

- Single-level disc surgery
- Randomized (1:1)
  - Control: Surgery Alone (N=175)
  - Treatment: Surgery + Oxiplex Gel (N=177)
- Multicenter
  - 29 sites enrolled (no more than 24 active at any time)
- Follow-ups:
  - 1, 3, 6 months postoperatively

Noteworthy Inclusion Criteria

- Initial disc surgery
  - Unilateral herniation
  - Lumbar
- Lumbosacral radiculopathy
- LSOQ measurable pain and symptoms
- MRI or CT/myelogram confirmation
- Age: 18 to 70 years
- Non-operative treatment (2 weeks)

Noteworthy Exclusion Criteria

- Previous Lumbar Surgery
- Epidural Steroids <4 wks
- Scoliosis
- Myelogram or Lumbar Puncture
- Presence of Foramenal Stenosis
- Subject of worker's compensation claim
- Party to personal injury litigation
- Intraoperative:
  - Dural Entry
  - Spinal Fusion
  - Multilevel Involvement
  - Contralateral Exploration
  - Epidural Fat Placement
  - Steroids
  - Retention of Hemostat

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Schedule of Evaluations

Assessment	Visit				
	Preop.	Surgery	Postoperative		
			30 Days (3-6 wks)	3 Mos (10-14 wks)	6 Mos (22-28 wks)
Informed Consent	X				
Medical History/Demographics	X				
Eligibility Assessment	X	X			
Enrollment/Randomization		X			
LSOQ	X		X	X	X
Physical & Neurological Exam	X		X		X
Vital Signs	X		X		X
Hematology	X		X		X
Chemistry	X		X		X
Pregnancy Test	X				
Urinalysis	X		X		
Concomitant Therapy	X	X	X	X	X
Adverse Events	X	X	X	X	X

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Subject Accountability

- Intent-to-Treat, "ITT"
  - 352 subjects enrolled
  - Oxiplex n=177
  - Control n=175
- Evaluable
  - 339 subjects completed end-of-study LSOQ at any time after 6 months
  - Oxiplex n=171
  - Control n=168
- Completed Cases, "CC"
  - 286 subjects completed end-of-study within protocol-defined window (all had endpoints within the protocol window)
  - Oxiplex n=145
  - Control n=141

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FDA's Analysis Population

- FDA's "CC population" (n=334)
- Based on 286 (per-protocol 22-28 weeks) + 48 subjects who completed the end-of-study LSOQ out-of-protocol (as far out as 52 weeks)
- Attributing values collected beyond 28 weeks to a 6-month value is prone to error

After decompression surgery, outcomes should be measured within a maximum of 6 months after surgery.

Longer follow-ups may introduce error that influence patient's rating of "outcome," especially if based on self-ratings of **current pain**, disability, or quality of life.

Mannion AE and Elfering A. Predictors of surgical outcome and their assessment. Euro Spine J 15:S93-S108, 2006.

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Demographic Variables: Balanced

Characteristic	Oxiplex	Control	
Continuous Covariate Measures:	**Mean (SD) N**	**Mean (SD) N**	**P-value**
Age (yrs)	41.81 (10.53) 177	41.71 (10.66) 175	0.9278
Height (m)	1.73 (0.10) 177	1.72 (0.10) 175	0.6286
Weight (kg)	85.30 (19.10) 177	83.13 (20.43) 174	0.2574
BMI	28.45 (5.84) 177	27.75 (5.55) 174	0.4300
Pulse	74.21 (9.84) 175	75.48 (10.63) 168	0.2563
Blood Pressure			
Systolic	125.88 (16.86) 176	124.60 (15.82) 169	0.4585
Diastolic	78.53 (10.75) 176	77.76 (9.70) 169	0.3053
Respiration	16.61 (2.45) 167	16.51 (2.73) 167	0.9007
Categorical Measures:	**n/N (%)**	**n/N (%)**	**P-value**
Gender (Male)	87/177 (49.15)	98/175 (56.00)	0.2025
Race			
Caucasian	152/177 (85.88)	153/175 (87.43)	1.000
Other	25/177 (14.12)	22/175 (12.57)	

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Procedural Characteristics: Balanced

Characteristic	Oxiplex		Control		P-value
	n/N (%)	Missing	n/N (%)	Missing	
Operative Level: L4-L5 L5-S1	83/175 (47.43) 92/175 (52.57)	2	81/173 (46.82) 92/173 (53.18)	1	0.9149
Operative Site: Left Right Right/Left	104/177 (58.76) 72/177 (40.68) 1/177 (0.56)	0	102/174 (58.62) 72/174 (41.38) 0/174 (0.00)	0	1.0000
Macro/Micro Surgery: Macro Surgery Micro Surgery	86/177 (48.59) 91/177 (51.41)	0	87/174 (50.00) 87/174 (50.00)	0	0.8312
Prolonged Surgery Yes	2/177 (1.13)	0	6/174 (3.45)	0	0.1716
Anesthesia: General Spinal Other	173/177 (97.74) 3/177 (1.69) 1/177 (0.56)	0	171/174 (98.28) 3/174 (1.72) 0/174 (0.00)	0	1.0000
Hemostatic Agent Use: Yes Removed	113/177 (63.84) 112/112 (100.00)	0 1	115/174 (66.09) 112/115 (97.39)	0	0.7372 0.2468
Continuous Variables	**Mean (SD) N**	**Missing**	**Mean (SD) N**	**Missing**	**P-value**
Surgical Time (min)	69.93 (27.73) 177	0	71.87 (32.40) 174	0	0.8813
Estimated Blood Loss (ml)	66.91 (68.12) 173	4	75.85 (191.9) 174	0	0.8490

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Baseline Neurological Examination: Balanced

Characteristic	Oxiplex		Control		P-value
	n/N (%)	Not Assessed	n/N (%)	Not Assessed	
Clinical Presentation:					
Pain Radiating to or Past the Knee with Neurological Signs	143/176 (81.25)	1	137/175 (78.29)	1	0.5990
Pain Radiating Past the Knee with w/o Neurological Signs	29/176 (16.48)		31/175 (17.71)		
	4/176 (2.27)		7/175 (4.00)		
Deep Tendon Reflexes:					
Right Patella Present	164/176 (93.18)	1	164/175 (93.71)	1	1.0000
Right Achilles Present	143/176 (81.25)	1	139/175 (79.43)	1	0.6889
Left Patella Present	161/176 (91.48)	1	157/174 (90.23)	1	0.7143
Left Achilles Present	136/176 (77.27)	1	124/174 (71.26)	1	0.2220
Sensory Examination:					
L4 Right Reduced	5/176 (2.84)	1	7/175 (4.00)	1	0.5737
L4 Left Reduced	13/177 (7.34)	0	15/174 (8.62)	0	0.6974
L5 Right Reduced	22/177 (12.43)	0	35/175 (20.00)	0	0.0605
L5 Left Reduced	51/177 (28.81)	0	37/175 (21.14)	0	0.1106
S1 Right Reduced	26/177 (14.69)	0	33/175 (18.86)	0	0.3200
S1 Left Reduced	42/177 (23.73)	0	35/174 (20.11)	0	0.4408
Motor Examination:					
Right Ant. Tibialis Abnormal	5/176 (2.84)	1	7/175 (4.00)	1	0.5737
Left Ant. Tibialis Abnormal	13/177 (7.34)	0	15/174 (8.62)	0	0.6974
Rt. Gastrocnemius Abnormal	22/177 (12.43)	0	35/175 (20.00)	0	0.0605
Lt. Gastrocnemius Abnormal	51/177 (28.81)	0	37/175 (21.14)	0	0.1106
Rt. Ext.Hal.Longus Abnormal	26/177 (14.69)	0	33/175 (18.86)	0	0.3200
Lt. Ext.Hal.Longus Abnormal	42/177 (23.73)	0	35/174 (20.11)	0	0.4408

* From Panel Pack Table 8.4

55

Maintaining the Study Blind

- Subjects randomized intraoperatively
- Blinded throughout study
  - Subjects
  - Clinical evaluators (not the surgeon)
  - LSOQ interviewers
- Randomization provided to statistical group only after database lock

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Oxiplex®

Clinical Safety

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Kansas City, KS

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Safety: Outside United States Experience

- Six years of experience (2002 – 2008)
- Over 100,000 spine procedures outside U.S.
- No adverse events attributable to the device

Post-Market Surveillance

- Feedback reports
- Field sales training
- Distributor & third-party audits
- Surgeon communication

DePuySpine, a Johnson & Johnson company | Medtronic

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Oxiplex® Studies
All Confirm Safety & Effectiveness

Author	Country	Study	# Subjects		
Peer-Review Publications			**Oxiplex**	**Control**	**Journal**
R Assietti	Italy	Retrospective	35	35	Spine 2008
P Fransen	Belgium	Prospective	396	62	Annals Surgical Innov Res 2008
K Kim et al	USA	Prospective	23	11	Neurosurgical Focus 2004
K Kim et al	USA	Retrospective	23	11	Spine 2003
Society Presentations & Posters			**Oxiplex**	**Control**	**Meeting**
P Fransen	Belgium	Retrospective	350	62	AANS 2007 Wash DC
A. Agarwal	UK	Prospective	180	180	ISSLS 2007 Hong Kong
Z. Zuki	Malaysia	Prospective	55	n/a	MOA 2006 Kuala Lumpur
P Fransen	Belgium	Retrospective	246	62	EANS 2006 Luxembourg
R Assietti	Italy	Prospective	15	15	CNS 2006 Chicago
G Guizzardi	Italy	Prospective	35	35	CNS 2006 Chicago
P Simons	Germany	Retrospective	90	90+90	CNS 2004 San Fran.
A DeMeeus	Belgium	Retrospective	20	62	BSN 2004 Leuven

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Pivotal Study Clinical Assessments

- Adverse Events (AEs)
- Laboratory Tests
- Concomitant Therapies
- Physical Examinations
- Neurological Examinations
  - Motor
  - Sensory

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Treatment Emergent Adverse Events (ITT)

	Oxiplex	Control	Total Subjects
Subjects Randomized	177	175	352
Subjects with any AE(s)	163 (92.1%)	153 (87.4%)	316 (89.8%)
Total Number of Reported AEs	685	738	1423
Total Number of Unique AEs	119	122	241
Number of AEs by Relationship to Device	621	657	1278
None	454 (73.1%)	529 (80.5%)	983 (76.9%)
Unlikely	160 (25.8%)	128 (19.5%)	288 (22.5%)
Possible	4 (0.6%)	0 (0.0%)	4 (0.3%)
Probable	3 (0.5%)	0 (0.0%)	3 (0.2%)
Definite	0 (0.0%)	0 (0.0%)	0 (0.0%)
Number of AEs by Severity	621	657	1278
Mild	323 (52.0%)	335 (51.0%)	658 (51.5%)
Moderate	232 (37.4%)	252 (38.4%)	484 (37.9%)
Severe	64 (10.3%)	63 (9.6%)	127 (9.9%)
Life threatening	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fatal	0 (0.0%)	1 (0.1%)	1 (0.1%)
Unknown	2 (0.3%)	6 (0.9%)	8 (0.6%)
Subjects with any SAE	13 (7.3%) P = 0.8438	14 (8.0%)	27 (7.7%)
Total Number of Serious AEs	19	16	35
Total Number of Unique Serious AEs	15	11	26
Number of Subjects Withdrawn for AEs	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Summary of Adverse Events by Relation to Device (ITT)

Relationship	Intensity	Site	Subject	Postop Onset	Duration	P-Value	Comment
Definite (none)	N/A	N/A	N/A	N/A	N/A	N/A	None
Probable						1.0000	
Nausea	Mild	A	A20	Day of Surgery	Day of Surgery		Spontaneous Resolution
Dizziness	Mild	A	A20	Day of Surgery	Day of Surgery		Spontaneous Resolution
Back Pain	Mild	A	A20	Day of Surgery	1 week		Spontaneous Resolution
Possible						0.1229	
Difficulty with Urinating	Moderate	B	B13	6 Weeks	Ongoing		Prostatitis
Low Back Pain	Severe	C	C08	5 Weeks	8 Weeks		Spontaneous Resolution
Recurrent HNP	Severe	D	D18	4 Months	Ongoing		Conservative Treatment
Delayed Wound Healing	Mild	E	E08	4 Weeks	7 Weeks		Retained Suture Removed

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Summary of Adverse Events by Relation to Device (ITT)

Preferred Term	# Oxiplex (n=177)	# Control (n=175)	# Total (n=352)
Intervertebral Disc Protrusion (Recurrent HNP)	4	9	13
Intervertebral Disc Disorder	0	2	2
Intervertebral Disc Degeneration	0	1	1

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Incidence of AEs Occurring ≥5 %

	Oxiplex	%	Control	%	Total Subjects	%
Subjects randomized	N=177		N=175		N=352	
Subjects reporting any AEs	n=163		n=153		n=316	
System Organ Class / Preferred Term						
Gastrointestinal Disorders						
Constipation	12	6.8%	6	3.4%	18	5.1%
Nausea	35	19.8%	36	20.6%	71	20.2%
Vomiting	10	5.6%	9	5.1%	19	5.4%
General Disorders & Administrative Site Conditions						
Chills	8	4.5%	8	4.6%	16	4.5%
Pyrexia	8	4.5%	11	6.3%	19	5.4%
Injury, Poisoning, Procedural Complications						
Incision Site Complication	57	32.2%	69	39.4%	126	35.8%
Procedural Pain	56	31.6%	54	30.9%	110	31.3%

(Continued)

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Incidence of AEs Occurring ≥5 % (continued)

System Organ Class / Preferred Term	Oxiplex	%	Control	%	Total Subjects	%
Musculoskeletal, Connective Tissue Disorders						
Arthralgia	12	6.8%	12	6.9%	24	6.8%
Back Pain	44	24.9%	39	22.3%	83	23.6%
Buttock Pain	12	6.8%	13	7.4%	25	7.1%
Intervertebral Disc Protrusion	4	2.3%	9	5.1%	13	3.7%
Muscle Spasm	25	14.1%	31	17.7%	56	15.9%
Muscular Weakness	9	5.1%	9	5.1%	18	5.1%
Musculoskeletal Stiffness	9	5.1%	5	2.9%	14	4.0%
Myalgia	6	3.4%	13	7.4%	19	5.4%
Pain in Extremity	26	14.7%	38	21.7%	64	18.2%
Nervous System Disorder						
Dizziness	10	5.6%	8	4.6%	18	5.1%
Headache	14	7.9%	12	6.9%	26	7.4%
Hypoaesthesia	18	10.2%	26	14.9%	44	12.5%
Hyporeflexia	9	5.1%	4	2.3%	13	3.7%
Sensory Loss	4	2.3%	8	4.6%	12	3.4%
Psychiatric Disorders						
Insomnia	12	6.8%	7	4.0%	19	5.4%
Skin and Subcutaneous Tissue Disorders						
Pruritis	8	4.5%	6	3.4%	14	4.0%

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Abnormal Physical Exam at 1 Month

Body System	P Value	Oxiplex	Control	Total Subjects
Subjects Randomized		177	175	352
Subjects with Physical Ex		173	169	342
Musculoskeletal	0.0728	26 (15.0%)	39 (23.1%)	65 (19.0%)
Heart/Cardiovascular	0.1180	1 (0.6%)	5 (3.0%)	6 (1.8%)
Ears,Eyes,Nose,Throat	0.1956	5 (2.9%)	10 (5.9%)	15 (4.4%)
Neurological (non-lower spine)	0.2669	36 (20.8%)	27 (16.0%)	63 (18.4%)
Skin	0.4910	12 (6.9%)	8 (4.7%)	20 (5.8%)
Lymph Nodes	0.4942	0 (0.0%)	1 (0.6%)	1 (0.3%)
Head,Neck,Thyroid	0.6820	2 (1.2%)	3 (1.8%)	5 (1.5%)
Abdomen	1.0000	5 (2.9%)	4 (2.4%)	9 (2.6%)
General Appearance	1.0000	10 (5.8%)	9 (5.3%)	19 (5.6%)
Lungs	1.0000	2 (1.2%)	2 (1.2%)	4 (1.2%)

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Abnormal Physical Exam at 6 Months

Body System	P Value	Oxiplex	Control	Total Subjects
Subjects Randomized		177	175	352
Subjects with Physical Ex		140	144	284
Musculoskeletal	0.0769	22 (15.7%)	35 (24.3%)	57 (20.1%)
Heart/Cardiovascular	0.2140	1 (0.7%)	5 (3.5%)	6 (2.1%)
Neurological (non-lower spine)	0.3623	44 (31.4%)	38 (26.4%)	82 (28.9%)
Ears,Eyes,Nose,Throat	0.4419	6 (4.3%)	10 (6.9%)	16 (5.6%)
Skin	0.4834	11 (7.9%)	8 (5.6%)	19 (6.7%)
Lungs	0.4983	0 (0.0%)	2 (1.4%)	2 (0.7%)
Abdomen	0.5366	6 (4.3%)	4 (2.8%)	10 (3.5%)
Lymph Nodes	1.0000	0 (0.0%)	1 (0.7%)	1 (0.4%)
General Appearance	1.0000	7 (5.0%)	7 (4.9%)	14 (4.9%)
Head,Neck,Thyroid	1.0000	2 (1.4%)	3 (2.1%)	5 (1.8%)

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Reoperations

Lower Incidence in Oxiplex Group

	P Value	Oxiplex N (%)	Control N (%)	Total Subjects N (%)
Subjects Randomized	0.190	177	175	352
Reoperation (0 - 3 months)	0.067	1 (0.6%)	6 (3.4%)	7 (2.0%)
Reoperation (3 - 6 months)	N/A	0	0	0
Total	0.067	1 (0.6%)	6 (3.4%)	7 (2.0%)

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Primary Safety Summary

- Adverse Events
  - No significant difference between Oxiplex & Control groups
  - No AEs led to discontinuation of any subject or discontinuation of the study
- Serious Adverse Events
  - No significant difference between Oxiplex & Control groups
  - No SAEs related to Oxiplex

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Secondary Safety Summary

- No significant differences in laboratory values & vital signs between Oxiplex and Control groups
- Good balance between concomitant therapies received by both groups
- Fewer neurological complications in Oxiplex group compared to Control group
- Fewer musculoskeletal abnormalities in Oxiplex group compared to Control group
- No post-op CSF leaks in Oxiplex subjects, compared to 2 in Controls
- Fewer reoperations in Oxiplex group compared to Control group (1 vs. 6)

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Safety Conclusions

- In the pivotal study
  - No safety issues in Oxiplex subjects across all measures
  - Oxiplex provided additional benefits vs. surgery alone
- Safety results in pivotal study are consistent with over 100,000 procedures outside U.S. and 6 years market experience
- Results demonstrate reasonable assurance that Oxiplex is safe for its intended use

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Oxiplex®

Statistical Methods

Richard Chiacchierini, Ph.D.
R.P. Chiacchierini
& Associates, LLC

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Statistical Analysis Plan

- Hypothesis
  - Oxiplex subjects would have greater improvement in leg pain from baseline compared to Controls
- Study Populations
  - Intent-to-Treat (ITT): All randomized subjects (n=352)
  - Completed Cases (CC): Per-protocol within window (n=286)
- Analysis
  - Multivariate, longitudinal analysis of the change in leg pain from baseline to six months by GEE
  - All clinically relevant baseline variables were included as potential covariates
  - Pre-specified global interactions between Oxiplex treatment and baseline covariates
  - Screened potential covariates by method of Hosmer and Lemeshow (2000)

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Baseline LSOQ Values (ITT)

Balanced Between Groups

	Oxiplex	Control	
Characteristic	**Mean (SD) N**	**Mean (SD) N**	**P-Value**
Leg Pain	67.54 (15.17) 177	67.74 (14.14) 174	0.9554
Back Pain	59.16 (20.87) 177	59.44 (21.77) 174	0.6576
Leg Weakness	3.53 (0.51) 177	3.50 (0.50) 174	0.5262
Symptoms	64.56 (16.70) 177	62.18 (16.41) 174	0.1737
Disability Days	8.34 (8.98) 177	7.48 (9.22) 174	0.3755
Activity Index	46.30 (5.66) 166*	46.43 (6.05) 168	0.7606
Patient Satisfaction	Not assessed at baseline		

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Univariate Unadjusted Means of Leg Pain Improvement (ITT)

Visit	Oxiplex Composite Leg Pain Mean (SD) N (LCL, UCL)	Control Composite Leg Pain Mean (SD) N (LCL, UCL)	Oxiplex Leg Pain Improvement from Baseline Mean (SD) N (LCL, UCL)	Control Leg Pain Improvement from Baseline Mean (SD) N (LCL, UCL)	Oxiplex – Control Improvement = Tx Effect Mean (LCL, UCL)
Baseline	67.54 (15.2) 177 (65.29, 69.79)	67.74 (14.1) 174 (65.62, 69.85)	N.A.	N.A.	N.A.
Month 1	21.58 (19.9) 177 (18.63, 24.54)	21.59 (21.5) 174 (18.38, 21.45)	45.95 (22.8) 177 (42.57, 49.34)	46.14 (24.3) 174 (42.51, 49.77)	-0.189 (-5.13, 4.75)
Month 3	15.96 (22.9) 177 (13.12, 18.80)	16.40 (20.6) 174 (13.32, 19.49)	51.58 (24.9) 177 (48.18, 54.98)	51.33 (24.9) 174 (47.60, 55.07)	0.243 (-4.79, 5.27)
Month 6	15.58 (19.7) 177 (12.66, 18.50)	17.52 (22.5) 174 (14.16, 20.89)	51.96 (23.7) 177 (48.45, 55.47)	50.21 (25.7) 174 (46.37, 54.06)	1.75 (-3.43, 6.93)

Univariate unadjusted means showed an improvement in leg pain that favored Oxiplex at 3 and 6 months

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Statistical Analysis Key Steps (ITT)

Step 1	Step 2	Step 3	Step 4	Step 5
Imputation for Missing Values	**Univariate Screening**	**Primary Multivariate Analysis** •Parsimonious final model •Identified interactions	**Interpretation of Categorical Interactions** •Self-defined subgroups	**Interpretation of Quantitative Interactions** •Regression •Analysis by subgroup •Analysis by time pt. •Sensitivity Analysis

- Screening cut-off P-value=0.15
- 8 main effects & 11 interactions (6 baseline covariates)
- Parsimonious multivariate model
- Pre-specified, manual backward elimination
- Treatment interactions required further analysis
- Clinically important subgroups identified
- Valid protection against post hoc analyses

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Final Model for Leg Pain (ITT)

Source	DF	Chi-Square	Pr > Chi Square
Treatment	1	11.52	0.0007
Visit	2	32.09	<0.0001
Baseline Leg Pain LSOQ Score	1	76.85	<0.0001
Baseline Back Pain LSO			0.4144
Baseline Back Pain by T			0.0113
Baseline Function LSOQ			0.0009
Study Site			0.0279
History of Pulmonary Ab			0.0309
History of GI Abnormalit			0.6463
GI Abnormality by Treatr			0.0055
History of Hematologic/I			0.0344
L5 Right	1	0.78	0.3775
L5 Right by Treatment Interaction	1	6.74	0.0094
L4 Left	1	0.10	0.7546
L4 Left by Treatment Interaction	1	5.10	0.0240
L5 Left	1	11.08	0.0009
L5 Left by Treatment Interaction	1	4.86	0.0274
Sexual Function	1	3.80	0.0511
Sexual Function by Treatment Interaction	1	5.96	0.0147

The site-by-treatment interaction term did not survive screening. It had a P-value of 0.64

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Interactions by Treatment - Leg Pain (ITT)

Quantitative (0-100)	Group	N	Interaction P-Value
Baseline Back Pain	Oxiplex (n)	177	0.0113
	Control (n)	174	

Baseline Finding Categorical (Normal vs. Abnormal)	Group	Normal (n)	Abnormal (n)	Interaction P-Value
GI History	Oxiplex (n)	117	60	0.0055
	Control (n)	119	55	
Neuro Exam L5 Right	Oxiplex (n)	155	22	0.0094
	Control (n)	140	34	
Neuro Exam L4 Left	Oxiplex (n)	164	13	0.0240
	Control (n)	159	15	
Neuro Exam L5 Left	Oxiplex (n)	126	51	0.0274
	Control (n)	137	37	
Sexual Function	Oxiplex (n)	161	16	0.0147
	Control (n)	156	18	

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Change in Leg Pain with Baseline Back Pain as a Function of Treatment

Population	Group	Patient Visits	Slope Regression Coefficient (SE)	P-Value for Slope	P-Value for Slope Difference
Over All Visits					
ITT	Oxiplex	531	-0.3363 (0.0463)	<0.0001	**0.0206**
	Control	522	-0.1781 (0.0499)	0.0004	
At 6-Month Visit					
ITT	Oxiplex	177	-0.3331 (0.0818)	<0.0001	**0.0537**
	Control	174	-0.0976 (0.0897)	0.2780	
CC	Oxiplex	145	-0.3745 (0.0857)	<0.0001	**0.0158**
	Control	141	-0.0704 (0.0912)	0.4414	

Regressions for Change in Leg Pain Averaged over Time and at 6 Months, by Treatment Group in ITT & CC Populations

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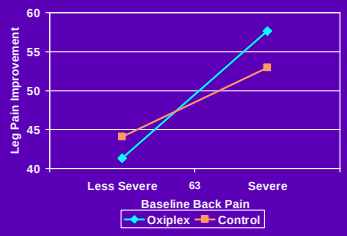
Interaction of Leg Pain with Baseline Back Pain (ITT)



Interaction on Improvement in Leg Pain from Baseline to 6 Months by Treatment and Baseline Back Pain (ITT)

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Sensitivity Analysis

Sensitivity of Baseline Back Pain Scores to Statistical Significance of the Change in Leg Pain at 6 Months for Various Back Pain Thresholds (CC)

Baseline Back Pain	Difference In Means of Leg Pain (95% CL)	Oxiplex Mean [%] (SD) N	% of Pop	Control Mean [%] (SD) N	% of Pop	P-value
≥ 63	9.58 (2.11, 17.04)	62.05 [82.1] (19.91) 78	54%	52.47 [70.7] (26.78) 78	55%	0.0123
≥ 62	9.58 (2.11, 17.04)	62.05 [82.1] (19.91) 78	54%	52.47 [70.7] (26.78) 78	55%	0.0123
≥ 61	9.58 (2.11, 17.04)	62.05 [82.1] (19.91) 78	54%	51.96 [71.5] (26.92) 90	64%	0.0123
≥ 60	7.45 (0.16, 14.75)	59.41 [80.3] (22.13) 88	61%	51.96 [71.5] (26.92) 90	64%	0.0454
≥ 59	7.45 (0.16, 14.75)	59.41 [80.3] (22.13) 88	61%	51.96 [71.5] (26.92) 90	64%	0.0454
≥ 58	**7.45 (0.16, 14.75)**	**59.41 [80.3] (22.13) 88**	**61%**	**51.96 [71.5] (26.92) 90**	**64%**	**0.0454**
≥ 57	6.96 (-0.08, 14.00)	58.70 [79.9] (21.79) 94	65%	51.74 [71.4] (26.76) 93	66%	0.0529

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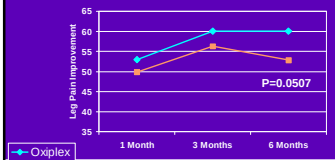
Improvement in Leg Pain (ITT) Over Time

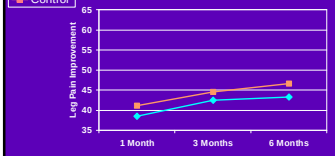
Most Prominent Improvement for Oxiplex Subjects Demonstrated at 6 Months in Subjects with Severe Baseline Back Pain



Subjects with Severe Baseline Back Pain (≥63)

1. Greater leg pain improvement for Oxiplex subjects increased over time.
2. Most prominent improvement for Oxiplex subjects was at 6 months.

Oxiplex
Control



Subjects with Less Severe Baseline Back Pain (<63)

1. Similar results for both groups.
2. No statistically significant difference between groups.

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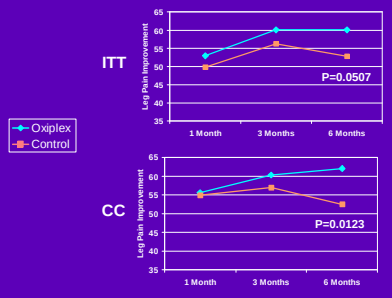
Leg Pain Improvement (ITT and CC) Over Time

Subjects with Severe Baseline Back Pain



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Secondary Endpoint Analysis: Back Pain

- Change in Back Pain from Baseline to 6 months analyzed in the same way as leg pain
- Screening resulted in 9 main effects and 12 interactions having p-values less than 0.15.
- The 12 main effects for these interaction terms must also be added.

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Final Model for Back Pain

Source	Degrees of Freedom	Chi-Square	Pr > Chi Square
Treatment	1	16.65	<0.0001
Study Visit (Time)	2	13.59	0.0011
Back Pain LSOQ Score	1	65.67	<0.0001
Back Pain by Treatment Interaction	1	11.37	0.0007
Function LSOQ Score	1	9.88	0.0017
CPT (Macro or Micro)	1	8.59	0.0034
History of a GI Abnormality	1	0.33	0.5633
GI Abnormality by Treatment Interaction	1	11.49	0.0007
Straight Leg Raise (Neuro Exam)	2	10.27	0.0059
Sexual Function (Subject Assessment)	1	0.01	0.9159
Sexual Function by Treatment Interaction	1	6.34	0.0118

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Interactions by Treatment – Back Pain (ITT)

Quantitative (0-100)	Group	N	Interaction P-Value
Baseline Back Pain	Oxiplex (n)	177	0.0007
	Control (n)	174	

Baseline Finding Categorical (Normal vs. Abnormal)	Group	Normal (n)	Abnormal (n)	Interaction P-Value
GI History	Oxiplex (n)	117	60	0.0007
	Control (n)	119	55	
Sexual Function	Oxiplex (n)	161	16	0.0118
	Control (n)	156	18	

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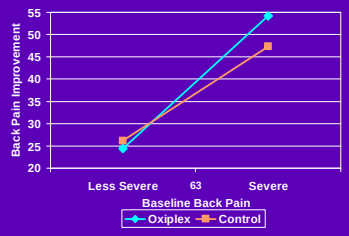
Interaction of Back Pain with Baseline Back Pain (ITT)



Interaction on Improvement in Back Pain from Baseline to 6 Months by Treatment and Baseline Back Pain (ITT)

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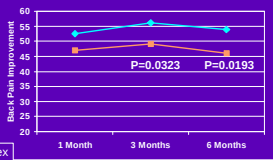
Improvement in Back Pain (ITT) Over Time

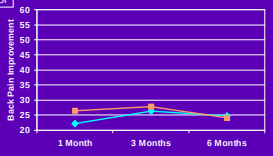
Most Prominent Improvement for Oxiplex Subjects Demonstrated at 3 & 6 Months in Subjects with Severe Baseline Back Pain



Subjects with Severe Baseline Back Pain (≥63)

1. Greater back pain improvement for Oxiplex subjects increased over time.
2. Improvements at 3 and 6 months were statistically significant.

Oxiplex
Control



Subjects with Less Severe Baseline Back Pain (<63)

1. Similar results for both groups.
2. No statistically significant difference between groups.

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Summary of Multivariate Analysis

- Multivariate analysis
  - The approved and appropriate method to interpret this clinically complex condition
- Important subgroup identified and analyzed
  - Subjects with severe back pain at baseline (the majority)
    - Leg pain – statistically significant improvement
      - ITT: P=.0507 at 6 months
    - Back pain – statistically significant improvement
      - ITT: P=.0323 at 3 months
      - ITT: P=.0193 at 6 months
- Subgroup results in ITT confirmed in CC population
- Oxiplex patients have twice the rate of improvement in leg pain as Controls for each unit of baseline back pain

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Oxiplex®

Clinical Effectiveness

Scott L. Blumenthal, M.D.
Texas Back Institute
Plano, TX

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Oxiplex Improved Clinical Outcomes

- Consistent clinical benefit from the use of Oxiplex in the majority of patients
  - Improvement in leg pain
  - Reduction in back pain
  - Fewer disability days
  - Enhanced patient satisfaction

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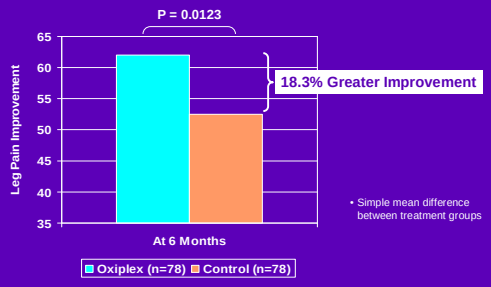
Leg Pain: Oxiplex vs. Surgery Alone

Greater Improvement for Oxiplex Relative to Control
Subjects with Severe Baseline Back Pain at 6 Months (CC)



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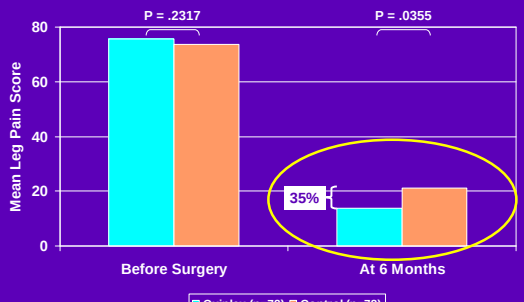
Leg Pain: Oxiplex vs. Surgery Alone

Greater Residual Pain Reduction in Oxiplex Compared to Control
Subjects with Severe Baseline Back Pain at 6 Months (CC)



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LSOQ Case Report Form – Leg Pain at Baseline

Pivotal Study Subjects

BASELINE

9.	Which word best describes the severity of the pain in your legs or buttocks, when it hurts the most ?					
	No pain ☐1	Mild ☐2	Discomforting ☐3	Distressing ☐4	Horrible ☐5	Excruciating ☒6
10.	Which word best describes the severity of the pain in your legs or buttocks, when it hurts the least ?					
	No pain ☐1	Mild ☐2	Discomforting ☐3	Distressing ☒4	Horrible ☐5	Excruciating ☐6
11.	Which word best describes the severity of the pain in your legs or buttocks, at this moment ?					
	No pain ☐1	Mild ☐2	Discomforting ☐3	Distressing ☐4	Horrible ☒5	Excruciating ☐6
12.	Which word best describes the severity of the pain in your legs or buttocks, on average, on a typical day ?					
	No pain ☐1	Mild ☐2	Discomforting ☐3	Distressing ☐4	Horrible ☒5	Excruciating ☐6
13.	Which word best describes the severity of the pain in your legs or buttocks, at the end of an active day ?					
	No pain ☐1	Mild ☐2	Discomforting ☐3	Distressing ☐4	Horrible ☐5	Excruciating ☒6
14.	Which word best describes the severity of the pain in your legs or buttocks, when you first wake up from a night's sleep ?					
	No pain ☐1	Mild ☐2	Discomforting ☐3	Distressing ☐4	Horrible ☒5	Excruciating ☐6

SCORE: 83

(((Sum of Questions 9-14) – 6] x 100) ÷ 30 = 83

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LSOQ Case Report Form – Leg Pain at 6 Months

Pivotal Study Subject

CONTROL

9.	Which word best describes the severity of the pain in your legs or buttocks, when it hurts the most ?					
	No pain ☐1	Mild ☐2	Discomforting ☒3	Distressing ☐4	Horrible ☐5	Excruciating ☐6
10.	Which word best describes the severity of the pain in your legs or buttocks, when it hurts the least ?					
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14.	Which word best describes the severity of the pain in your legs or buttocks, when you first wake up from a night's sleep ?					
	No pain ☐1	Mild ☒2	Discomforting ☐3	Distressing ☐4	Horrible ☐5	Excruciating ☐6

SCORE: 23

(((Sum of Questions 9-14) – 6] x 100) ÷ 30 = 23

95

LSOQ Case Report Form – Leg Pain at 6 Months

Pivotal Study Subject

OXIPLEX

9.	Which word best describes the severity of the pain in your legs or buttocks, when it hurts the most ?					
	No pain ☐1	Mild ☒2	Discomforting ☐3	Distressing ☐4	Horrible ☐5	Excruciating ☐6
10.	Which word best describes the severity of the pain in your legs or buttocks, when it hurts the least ?					
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	No pain ☒1	Mild ☐2	Discomforting ☐3	Distressing ☐4	Horrible ☐5	Excruciating ☐6
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	No pain ☐1	Mild ☒2	Discomforting ☐3	Distressing ☐4	Horrible ☐5	Excruciating ☐6
14.	Which word best describes the severity of the pain in your legs or buttocks, when you first wake up from a night's sleep ?					
	No pain ☒1	Mild ☐2	Discomforting ☐3	Distressing ☐4	Horrible ☐5	Excruciating ☐6

SCORE: 13

(((Sum of Questions 9-14) – 6] x 100) ÷ 30 = 13

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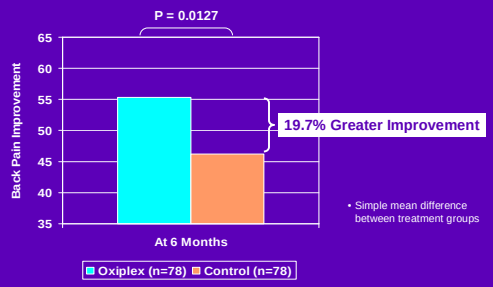
Back Pain: Oxiplex vs. Surgery Alone

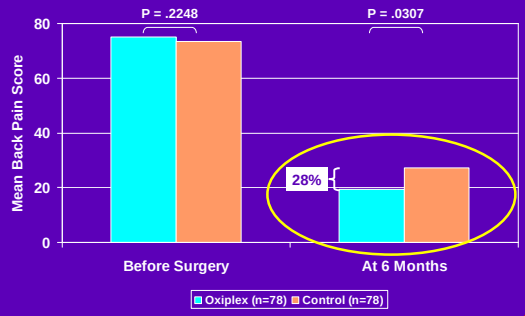
Greater Improvement for Oxiplex Relative to Control
Subjects with Severe Baseline Back Pain at 6 Months (CC)



97

Back Pain: Oxiplex vs. Surgery Alone

Greater Residual Pain Reduction in Oxiplex Compared to Control
Subjects with Severe Baseline Back Pain at 6 Months (CC)



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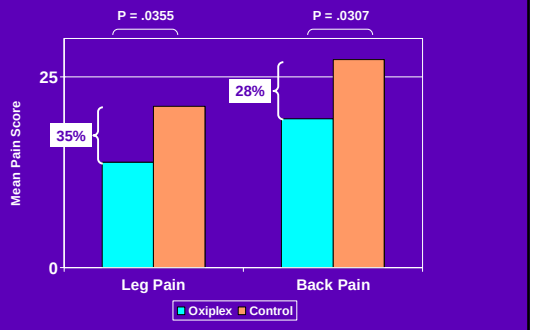
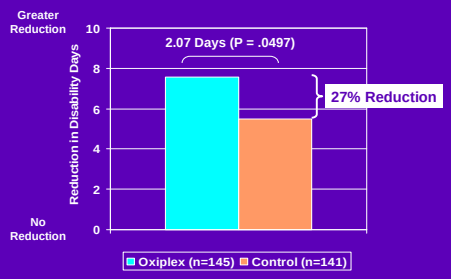
Additional Reduction in Leg and Back Pain at 6 Months in Subjects with Severe Baseline Back Pain (CC)



99

Disability Days

Fewer Disability Days in Oxiplex Subjects (CC)



Disability days defined as days when a patient is completely disabled by his/her lower back condition.

100

Patient Satisfaction

Greater Satisfaction for Oxiplex Subjects (CC)

Satisfaction at 6 Months by Treatment and Baseline Back Pain for Subjects with Severe Baseline Back Pain

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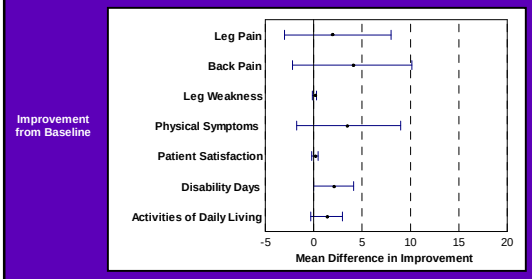
Consistent Clinical Benefit of Oxiplex®

All CC Subjects

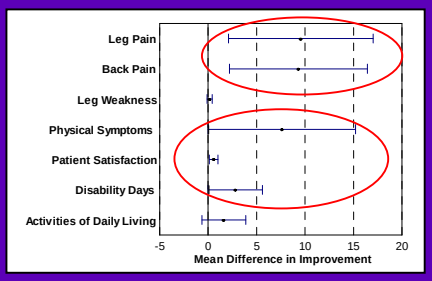
All 7 Endpoints Favor Oxiplex (P=0.049)



Means Differences and 95% Confidence Limits in Improvement between Oxiplex & Control Groups at 6 Months (CC)

102

Consistent Clinical Benefit in
CC Subjects with Severe Back Pain



Means Differences and 95% Confidence Limits in Improvement between Oxiplex & Control Groups at 6 Months (CC)

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Reasonable Assurance of Oxiplex Effectiveness

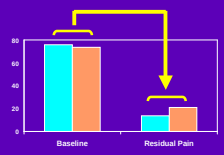
1. Greater Relative Reduction in Pain at 6 Months

Statistical Difference

		All	Severe Back Pain
Leg	ITT	0.5076	0.0507
	CC	0.3750	0.0123
Back	ITT	0.2782	0.0193
	CC	0.2065	0.0127

Clinical Significance (Magnitude of Effect)

		All	Severe Back Pain
Leg	ITT	3.5%	13.6%
	CC	4.9%	18.3%
Back	ITT	8.3%	17.1%
	CC	10.8%	19.7%



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Reasonable Assurance of Oxiplex Effectiveness

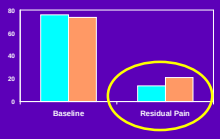
2. Relative Reduction in Residual Pain at 6 Months

Statistical Difference

		All	Severe Back Pain
Leg	ITT	0.3887	0.0972
	CC	0.4452	0.0355
Back	ITT	0.1537	0.0396
	CC	0.3706	0.0307

Clinical Significance (Magnitude of Effect)

		All	Severe Back Pain
Leg	ITT	11.1%	25.9%
	CC	11.0%	34.9%
Back	ITT	14.8%	24.8%
	CC	10.9%	28.4%



105

Reasonable Assurance of Oxiplex Effectiveness

3. Clinical Measures of Success

	Oxiplex vs. Control
Reduced Reoperation Rates	• 0.6% vs 3.4%
Reduced Incidence of Neurological Symptoms	• Pain 15% vs 22% • Hypoaesthesia 10% vs 15%
Reduced Incidence of Musculoskeletal Abnormalities	• 16% vs 24%
Patient Satisfaction	• 22.7% relatively greater
Disability Days	• 2 fewer days

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Oxiplex®

Summary of Safety & Effectiveness

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Reasonable Assurance of Oxiplex Safety
All Patients

- No significant difference in AEs and SAEs between Oxiplex & Control groups
- No SAEs related to Oxiplex
- Fewer neurological complications in Oxiplex group compared to Control group
- Fewer musculoskeletal abnormalities in Oxiplex group compared to Control group
- No CSF leaks in Oxiplex group
- Fewer reoperations in Oxiplex group (1) compared to Control group (6)
- 6 years of real-world experience: Over 100,000 procedures & no reported adverse events attributable to Oxiplex

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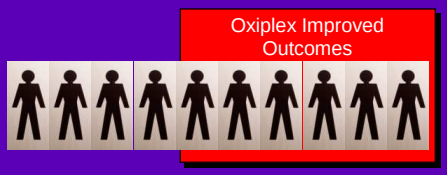
Reasonable Assurance of Oxiplex Effectiveness

- In a majority subgroup (severe back pain)
  - Significantly greater improvement in Leg Pain
  - Significantly greater improvement in Back Pain
  - Significantly greater level of Satisfaction



109

Reasonable Assurance of Oxiplex Effectiveness

- In all patients (regardless of baseline pain)
  - Greater reduction in Disability Days (CC)
  - Fewer neurological symptoms (ITT)
  - Fewer musculoskeletal abnormalities (ITT)
  - Fewer reoperations (ITT)

110

Study Success

- Primary endpoint: Improvement in Leg Pain from baseline to follow-up visit (1, 3, 6 mos.) as measured by the LSOQ.

Greater Relative Reduction in Leg Pain at 6 Months

		All	Severe Back Pain
Leg	ITT	0.5076	0.0507
	CC	0.3750	0.0123

- Secondary endpoint: Improvement in Back Pain from baseline to follow-up visit (1, 3, 6 mos.) as measured by LSOQ.

Greater Relative Reduction in Back Pain at 6 Months

		All	Severe Back Pain
Back	ITT	0.2782	0.0193
	CC	0.2065	0.0127

111

Study Success

Relative Difference in Residual Pain Scores between Oxiplex & Control Groups at 6 Months

		All	Severe Back Pain
Leg	ITT	11.1%	25.9%
	CC	11.0%	34.9%
Back	ITT	14.8%	24.8%
	CC	10.9%	28.4%

112

Safety and Effectiveness of Oxiplex

- There is reasonable assurance that Oxiplex is safe, based upon valid scientific evidence, that the probable benefits to health outweigh any probable risks.
- There is reasonable assurance that Oxiplex is effective, based upon valid scientific evidence, in a significant portion of the target population, and that the use of Oxiplex for its intended use provides clinically significant results.

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Oxiplex®

Reasonable Assurance of Safety & Effectiveness

Unmet Clinical Need

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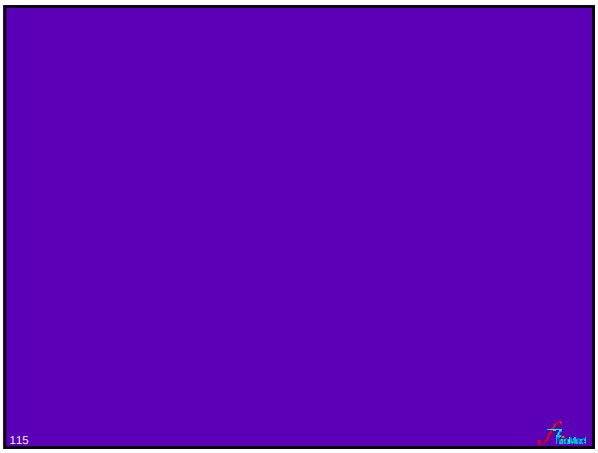
115